PATENT SPECIFICATION

NO DRAWINGS

Inventors: CHARLES FREDERICK HOWELL, ROBERT ALLIS HARDY and NICANOR QUINONES QUINONES

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Date of Application and filing Complete Specification: 23 Dec., 1966.

No. 57710/66.

Complete Specification Published: 14 Jan., 1970.

ERRATUM

SPECIFICATION NO. 1,177,956

Page 1, Heading Inventors:- *for* "ROBERT ALLIS HARDY" *read* "ROBERT ALLIS HARDY JR."

THE PATENT OFFICE
5 August 1970

R 128814/2

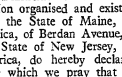
COMPLETE SPECIFICATION

Production of Oxazepines and Thiazepines

We, AMERICAN CYANAMID COMPANY, a corporation organised and existing under the Laws of the State of Maine, United States of America, of Berdan Avenue, Township of Wayne, State of New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

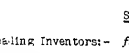
This invention relates to a process for preparing 11-tertiary-aminobenz [b,f][1,4] oxazepines and thiazepines.

The oxazepines and thiazepines with which this invention is concerned may be represented by the formula:



(I)

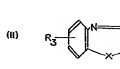
wherein X is an oxygen or sulfur; one of R_1 and R_2 is hydrogen, (C_1—C_6) alkyl, (C_1—C_6) alkoxy, halogen or trifluoromethyl, and the other of R_1 and R_2 is hydrogen, (C_1—C_6) alkoxy or halogen; Y is hydroxy, amino, (C_1—C_6)alkylamino, di-(C_1—C_6) alkylamino, 1-piperazinyl, 4-(C_1—C_6)-alkyl-1-piperazinyl, 4-hydroxy (C_1—C_6) alkyl-1-piperazinyl, pyrrolidino, (C_1—C_6) alkyl-pyrrolidino, piperidino, (C_1—C_6) alkylpiperidino, morpholino or (C_1—C_6) alkylmorpholino; R is (C_1—C_6) alkyl; n is 2, 3 or 4; or the group



taken together represents 1-piperazinyl, 4-(C_1—C_6) alkyl-1-piperazinyl, or 4-hydroxy (C_1—C_6) alkyl-1-piperazinyl.

The compounds of Formula I above are physiologically active on the central nervous system. They show high activity as tranquillizers at non-toxic doses and in some instances anti-depressant properties at dosage levels which produce neither overt stimulation nor depression.

In accordance with this invention, compounds of Formula I are prepared by a process which comprises (a) diazotizing a compound of the formula:



(II)

wherein one of R_3 and R_4 is hydrogen, halogen, (C_1—C_6) alkyl, (C_1—C_6)alkoxy or trifluoromethyl, and the other of R_3 and R_4

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Index at acceptance: —**C2 C**(1E5K4, 1E6K4, 1G5A, 1G5B, 1G6A2, 1G6B3, 1G6B6, 1H1A3, 1H1B, 1H1C3, 1Q1A, 1Q6C, 1Q8A, 1Q11B, 1Q11D, 1Q11G, 1Q11J, 2A3, 2A7, 2A8, 2A10, 2A13, 2A14, 2R15 2R17, 3A13C1C, 3A13C10B, 3A13C10H, B4A1, B4D, B4E, 213, 215, 246, 247, 25Y, 250, 252, 255, 28X, 30Y, 305, 32Y, 323, 332, 36Y, 364, 43X, 45Y, 456, 50Y, 500, 670, 671, 672, 681, 708, 79Y, 790, 17X-186-272, 170-189-276, 18X-195-275, LH, ML); **A5 B**(38Y, 383, 392, 42Y, 420, 44Y, 442, 45Y, 451, 48Y, 480, 482, 51Y, 511, 54Y, 541, 542, 544, 55Y, 554, 556, 56Y, 565, 566, 57Y, 577, 61Y, 616, 67Y, 67X, 670)

International Classification: —**C 07 d 87/54, 99/02**

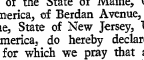
COMPLETE SPECIFICATION

Production of Oxazepines and Thiazepines

We, AMERICAN CYANAMID COMPANY, a corporation organised and existing under the Laws of the State of Maine, United States of America, of Berdan Avenue, Township of Wayne, State of New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a process for preparing 11-tertiary-aminobenz [b,f][1,4] oxazepines and thiazepines.

The oxazepines and thiazepines with which this invention is concerned may be represented by the formula:



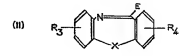
(I)

wherein X is an oxygen or sulfur; one of R_1 and R_2 is hydrogen, (C_1—C_6) alkyl, (C_1—C_6) alkoxy, halogen or trifluoromethyl, and the other of R_1 and R_2 is hydrogen, (C_1—C_6) alkoxy or halogen; Y is hydroxy, amino, (C_1—C_6)alkylamino, di-(C_1—C_6) alkylamino, 1-piperazinyl, 4-(C_1—C_6)-alkyl-1-piperazinyl, 4-hydroxy (C_1—C_6) alkyl-1-piperazinyl, pyrrolidino, (C_1—C_6) alkyl-pyrrolidino, piperidino, (C_1—C_6) alkylpiperidino, morpholino or (C_1—C_6) alkylmorpholino; R is (C_1—C_6) alkyl; n is 2, 3 or 4; or the

group taken together represents 1-piperazinyl, 4-(C_1—C_6) alkyl-1-piperazinyl, or 4-hydroxy (C_1—C_6) alkyl-1-piperazinyl.

The compounds of Formula I above are physiologically active on the central nervous system. They show high activity as tranquillizers at non-toxic doses and in some instances anti-depressant properties at dosage levels which produce neither overt stimulation norm depression.

In accordance with this invention, compounds of Formula I are prepared by a process which comprises (a) diazotizing a compound of the formula:



(II)

wherein one of R_3 and R_4 is hydrogen, halogen, (C_1—C_6) alkyl, (C_1—C_6)alkoxy or trifluoromethyl, and the other of R_3 and R_4

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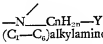
is amino; and E is the group



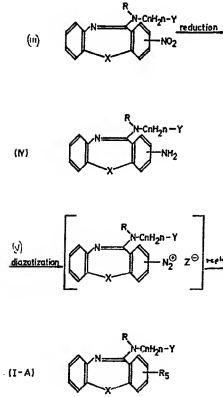
—N—C_nH_{2n}—Y or a hydroxy, amino, di-(C_1—C_6)alkylamino, or (C_1—C_6) alkylamino group;

(a) in the presence of a mineral acid with an alkali metal nitrite or alkaline earth metal nitrite, and subsequently treating the diazonium compound with a hydrohalic acid, a (C_1—C_6) alkanol or a reducing agent;

(b) when required, when E is hydroxy, amino, di-(C_1—C_6)alkylamino or (C_1—C_6) alkylamino, before or after step (a), converting E into the group

In a modification of this process both R_3 and R_4 in the starting compound of Formula II can be amino, so that in the product of Formula I, R_3 and R_4 are each hydrogen, (C_1—C_6) alkoxy or halogen.

More specifically, a preferred embodiment of this process of the invention is illustrated by the following reaction scheme:



wherein R, X, Y and n are as previously defined; Z is an anion of a mineral acid; and R_5 is hydrogen, halogen or (C_1—C_6) alkoxy. By this procedure, a nuclear substituted nitro derivative of an 11-*tertiary*-amino-dibenz-[b,f][1,4]oxazepine or thiazepine (III) is reduced to the corresponding nuclear substituted amino derivative (IV) by any one of several methods. Suitable procedures include catalytic hydrogenation in the presence of a metal catalyst; reduction by a metal, such as zinc or iron; reduction by a hydride, such as sodium borohydride; and reduction by inorganic reducing agents including, for example, stannous chloride. This reduction is generally carried out in a solvent at a temperature within the range of from about 0° to 100°C. The resulting nuclear substituted amino derivatives (IV) may be isolated and purified by methods well known to those skilled in the art, or, optionally, may be prepared and further used in the diazotization and replacement reactions without isolation or purification.

The diazotization of the nuclear substituted amino derivatives (IV) is generally effected in the presence of a mineral acid (HZ) such as hydrohalic acids, sulfuric acid, fluoroboric acid or phosphoric acid by the addition of an alkali metal or alkaline earth metal nitrite. These diazotizations are generally carried out in hydroxylic solvents such as water and (C_1—C_6) alkanols. Alternatively, the diazotization may be carried out by treating a mineral acid salt of the nuclear substituted amino derivative (IV) with an alkyl nitrite in the presence of a (C_1—C_6) alkanol. The diazotizations are preferably carried out at a temperature range from −25°C. to 25°C. The diazonium salts (V) produced by these procedures are, generally, unstable and reactive intermediates. Consequently, they are usually reacted "in situ", carrying out the replacement reaction without isolation of intermediates. In some cases, however, isolation of a diazonium salt (V), particularly in the presence of a stabilizing agent, such as fluoroborate salts, or stannic and cuprous salts, is possible and desirable. In these cases, the diazonium salt (V) is isolated from the diazotization reaction, and then further transformed by the replacement reaction.

The diazonium salt replacement is carried out in the presence of a hydrohalic acid, a (C_1—C_6) alkanol or a reducing agent. Treatment of the diazonium salt (V) with a hydrohalic acid produces a nuclear substituted halogen derivative (I—A, R_5=Halogen). This replacement reaction is conveniently carried out by the addition of a metal catalyst to a solution of the diazonium salt containing the desired halogen acid. Suitable catalysts include cuprous halides, copper metal, iron and cobalt halides. These replacement reactions are generally carried out

in an aqueous solvent at a temperature range from 0°C. to 100°C. until the evolution of nitrogen has ceased, indicating a substantially complete reaction. Additionally, formation of iodo derivatives (I—A, R_5=I) is often effected in the absence of a metal catalyst, and fluoro derivatives (I—A, R_5=F) may be obtained by heating a diazonium fluoborate intermediate.

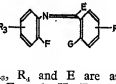
Treatment of the diazonium salt (V) with a (C_1—C_6) alkanol produces a nuclear substituted alkoxyl derivative [I—A, R_5=C_1—C_6) alkoxyl]. This replacement reaction is generally carried out with a diazonium salt prepared using a mineral acid of low nucleo-philicity, such as sulfuric acid or phosphoric acid. This conversion is effected either by formation of the diazonium salt in a (C_1—C_6) alkanol, or by the addition of an excess of a (C_1—C_6) alkanol to the diazonium solution, followed by heating. A suitable temperature range is from 25°C. to 125°C.

Treatment of the diazonium salt (V) with a suitable reducing agent produces an 11-*tertiary* - amino - dibenz[b,f][1,4]oxazepine or thiazepine containing a hydrogen (I—A, R_5=H) in place of the nuclear substituted diazonium moiety. Suitable reducing agents include hypophosphorous acid, (C_1—C_6) alkanols, such as ethanol, alkaline formaldehyde and alkali metal stannites. This replacement reaction is conveniently effected by the addition of the reducing agent to an aqueous solution of the diazonium salt. The temperature range is usually from 0°C. to 100°C.; a preferred range is from 0°C. to 25°C. allowing the reaction mixture to come to room temperature as the reaction proceeds and nitrogen is evolved.

When E in the formula (Formula II) of the starting compound is amino, di-(C_1—C_6) alkylamino or (C_1—C_6)alkylamino, it may be converted to the group

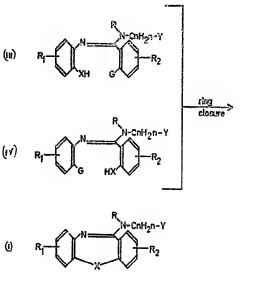
by the process which forms the subject of our co-pending Application No. 43667/69, Serial No. 1,177,957, divided herefrom.

The starting compounds of Formula II may be prepared by a process which comprises cyclizing a compound of the formula:



wherein R_3, R_4 and E are as defined in relation to Formula II; F or G is hydroxy or mercapto and the other is halo, nitro or diazonium, and wherein F and G may occupy interchanged positions; to form a heterocyclic ring wherein F and G together form an oxygen or sulfur atom.

More specifically, this process can be illustrated by the following 2 ring closure reactions:



where R, R_1, R_2, X, Y and n are as previously defined; and G is a halogen or nitro. The ring closure reaction is achieved by heating the substituted N-(1,N-diarylformimidoyl)-amine (intermediates III or IV) in an organic solvent. A polar solvent is generally employed to facilitate the reaction. Suitable solvents include formamide, dimethylformamide, dimethylacetamide, diethylacetamide, or diethylene-glycol monoethyl ether. The ring closure is usually carried out at an elevated temperature, conveniently the refluxing temperature of the solvent. Temperatures of from about 125°C. to about 200°C. are suitable, but the preferred temperature range is from about 150°C. to about 180°C. Heating is continued until the reaction is substantially complete, generally requiring from a few minutes to several hours or more.

In the above-described reaction, an alkaline condensing agent is preferably employed to promote ring closure in a reasonable period of time. Suitable condensing agents useful for these reactions are alkali or alkaline earth metal carbonates such as sodium carbonate, potassium carbonate, lithium carbonate, or magnesium carbonate. Alkali metal hydroxides such as sodium hydroxide or potassium hydroxide, may also be employed as alkaline condensing agents.

Alkali metal hydrides and amides including sodium hydride, lithium amide, are also useful. These alkaline condensing agents are generally used in approximately equivalent molecular proportions with the N-(1,N-diaryliformimidoyl)amine intermediates (III and IV). A metal catalyst may also be, optionally, employed to facilitate the ring closure reaction. Copper powder is particularly useful and copper salts are also successfully used.

As stated above, the compounds prepared by the process of the present invention are physiologically active on the central nervous system in that they show high activity as tranquilizers at non-toxic doses and in some instances anti-depressant properties at dosage levels which produce neither overt stimulation nor depression.

A useful test for tranquilizer activity consists of measuring the reduction of spontaneous motor activity in animals by means of an actophotometer (a photoelectric device for quantitatively measuring locomotor activity). Graded doses of the active compounds prepared by the process of this invention are administered to groups of mice, and the effective dosage range for a significant reduction of motor activity (a measure of tranquilization) compared to control groups is established.

The anti-depressant properties of the compounds prepared by the process of the present invention are evident by measuring their ability to counteract a depression induced in animals by the administration of tetrabenazine hexamate. Graded doses of the active compounds are administered to groups of mice, and this is followed by administering a dose of tetrabenazine which is known to markedly depress the exploratory behavior of normal mice. The anti-depressant treated groups show normal exploratory behavior, while the control groups, and groups treated with an ineffective anti-depressant agent do not show this normal exploratory behavior, but show well known profound depression induced by tetrabenazine. The results from several dose levels are used to establish effective dose ranges. The anti-depressant compounds prepared by the process of this invention show their desirable properties by this procedure at dose levels which produce little or no untoward reactions, such as ataxia or reduced spontaneous motor activity.

In addition, some of the compounds prepared by the process of this invention show other valuable pharmaceutical properties, such as analgesic activity.

The compounds prepared by the process of this invention are, in general, white crystalline solids only slightly soluble in water, but moderately soluble in organic solvents such as methanol or ethanol. They are basic substances which are usually soluble in aqueous mineral acids at room temperature. They form substantially insoluble acid addition salts such as, for example, the hydrochloride, sulfate, phosphate, citrate, tartrate, maleate or fumarate. The active compounds, generally in the form of their salts, may be administered orally or parenterally and when so administered are effective central nervous system agents. For oral administration, the compounds prepared by the process of this invention may be incorporated with the usual pharmaceutical excipients and used, for instance, in the form of tablets, capsules, dragees, liquids to be administered in drops, emulsions, suspensions and syrups, and in chocolate, candy or chewing gum. They may also be administered in aqueous solutions for parenteral injection.

The following examples illustrate in detail the preparation of representative 11-*tertiary*-aminodibenz[b,f][1,4]oxazepines and thiazepines by the process of this invention.

Example 1

Preparation of 2-Chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine

2 - Chloro - 2' - hydroxy - 5 - nitrobenzanilide is treated with phosphorus pentachloride in anhydrous benzene. The mixture is refluxed until it becomes homogeneous, and an excess of N-methylpiperazine is added. Refluxing is continued until the reaction is substantially complete, and 1-[1-(2-chloro-5-nitrophenyl) - N - (*o* - hydroxyphenyl)-formimidoyl]-4-methyl-piperazine is obtained. This intermediate is cyclized by heating in dimethylacetamide with anhydrous potassium carbonate and copper powder, and 2-nitro-11 - (4 - methyl - 1 - piperazinyl)dibenz-[b,f][1,4]oxazepine is, thereby, obtained.

A solution of 0.35 gram of crude 2-nitro-11 - (4 - methyl - 1 - piperazinyl)dibenz-[b,f][1,4]oxazepine prepared as described above, in 10 milliliters of 0.3 Normal hydrochloric acid is hydrogenated at atmospheric pressure over 3 milligrams of platinum oxide. The reduction requires about 3 hours when conducted with gentle warming from the magnetic stirring motor. When no more hydrogen is absorbed, the solution is treated with a little charcoal and filtered. The resulting pale yellow solution contains 2-amino-11-(4 - methyl - 1 - piperazinyl)dibenz[b,f][1,4]-oxazepine and is used in the next step without isolation.

The above solution is cooled to 0°—5°C. and treated with 52 milligrams of solid 95% sodium nitrite and 1 milliliter of concentrated hydrochloric acid. The cold solution is treated with an ice-cold solution of 90 milligrams of cuprous chloride in 1 milliliter of concentrated hydrochloric acid and then is stirred at room temperature to complete the gradual evolution of nitrogen gas. The solution is warmed to 60°C. to ensure comple-

tion of the reaction, cooled and washed with ether. Five milliliters of concentrated ammonium hydroxide and 15 milliliters of hexane are added and the entire mixture is filtered before separation of the organic phase. The hexane solution is chromatographed on alumina and 2-chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine is isolated from the eluate. This product melts at 108°—111°C. when recrystallized from hexane.

EXAMPLE 2

Preparation of 2-Chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine

A solution of 3.06 grams of 2-amino-11-(4 - methyl - 1 piperazinyl)dibenz[b,f][1,4]-oxazepine in 80 milliliters of 0.5 Normal hydrochloric acid (4 equivalents) is cooled to 0°—5°C. and treated with a solution of 0.73 grams of 95% sodium nitrite in 3 milliliters of water. The resulting diazonium salt solution is treated with about 1 gram of copper powder and warmed until evolution of gases (nitrogen) is complete. The mixture is filtered and the filtrate is washed with ether. The lower (aqueous) layer is made strongly basic by the addition of 10 milliliters of concentrated ammonium hydroxide. The resulting precipitate containing the desired product is collected and the product is purified by recrystallization or by chromatography. The resulting 2-chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine melts at 108°—111°C. when recrystallized from hexane.

EXAMPLE 3

Preparation of 11-(4-Methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine

A solution of 3.0 grams of 2-amino-11-(4-methyl - 1 - piperazinyl)dibenz[b,f][1,4]-oxazepine in 60 milliliters of 0.5 Normal hydrochloric acid is cooled to 0—5°C. and treated with 0.73 grams of solid sodium nitrite. The solution is then treated with about 1.2 grams of 30% aqueous hypophosphorous acid (5.3 molecular equivalents) and stirred at 0—5°C. until evolution of nitrogen is complete and the solution no longer gives a red color when a drop is treated with alkaline 2-naphthol-3,6-disulfonic acid (R-salt). The solution is washed with ether and made alkaline with 100 milliliters of 10% sodium hydroxide. The precipitated product is collected and purified by recrystallization or by chromatography as desired. 11-(4-Methyl-1-piperazinyl)dibenz-[b,f][1,4]oxazepine melts at about 97°—98°C. when recrystallized from petroleum ether.

EXAMPLE 4

Preparation of 2-Methoxy-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine

A solution of 3.0 grams of 2-amino-11-(4-methyl - 1 - piperazinyl)dibenz[b,f][1,4]-oxazepine in 10 milliliters of 3 Normal sulfuric acid kept at 0—5°C. by means of an ice-acetone bath is treated with 0.73 gram of solid 95% sodium nitrite in portions. The solution, diluted with 200 milliliters of absolute methanol, is heated under reflux until nitrogen is no longer evolved. The methanol is removed by distillation under reduced pressure. The residue is dissolved in 20 milliliters of water, washed with ether and made strongly basic with 15 milliliters of 10% sodium hydroxide. The precipitated 2 - methoxy - 11 - (4 - methyl - 1-piperazinyl)dibenz[b,f][1,4]oxazepine is purified by chromatography on alumina.

EXAMPLE 5

Preparation of 2-Chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]thiazepine

The procedure of Example 2 is repeated. 2 - amino - 11 - (4 - methyl - 1 - piperazinyl)-dibenz[b,f][1,4]thiazepine, is diazotized followed by subsequent treatment with cuprous chloride and hydrochloric acid, and 2-chloro-11 - (4 - methyl - 1 - piperazinyl)dibenz-[b,f][1,4]thiazepine is obtained. When purified by recrystallization from petroleum ether, this product melts at 114°—116°C.

EXAMPLE 6

Preparation of 2-Chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]thiazepine

The procedure of Example 1 is repeated. 11 - (4 - methyl - 1 - piperazinyl) - 2 - nitro-dibenz[b,f][1,4]thiazepine is reduced to the corresponding amino derivative, and this amino derivative is diazotized followed by treatment with copper powder and hydrochloric acid. The product 2-chloro-11-(4-methyl - 1 - piperazinyl)dibenz[b,f][1,4]thiazepine is obtained.

EXAMPLE 7

Preparation of 11-(4-Methyl-1-piperazinyl)-dibenz[b,f][1,4]thiazepine

11 - (4 - Methyl - 1 - piperazinyl) - 2-nitrodibenz[b,f][1,4]thiazepine is reduced with stannous chloride in the presence of hydrochloric acid to the corresponding amino derivative, and this amino derivative is diazotized followed by treatment with hypophosphorous acid, and 11-(4-methyl - 1 - piperazinyl)dibenz[b,f][1,4]-thiazepine is obtained.

EXAMPLE 8

Preparation of 2-Chloro-11-[4-(2-hydroxyethyl) - 1 - piperazinyl]dibenz[b,f][1,4]-thiazepine

Following the procedure of Example 7, 11 - [4 - (2 - hydroxyethyl) - 1 - piperazinyl]-2-nitrodibenz[b,f][1,4]thiazepine is reduced to the corresponding amino derivative, and this amino derivative is diazotized followed by treatment with cuprous chloride in hydrochloric acid. The product 2-chloro-11-[4-(2-

hydroxyethyl) - 1 - piperazinyldibenz[b,f]-[1,4]thiazepine is obtained.

Example 9

Preparation of 2-Chloro-11-[4-(2-hydroxyethyl)-1-piperazinyl]dibenz[b,f][1,4]oxazepine

Using the procedure of Example 1, 2-amino - 11 - [4 - (2 - hydroxyethyl) - 1-piperazinyl]dibenz[b,f][1,4]oxazepine is diazotized, followed by decomposition in the presence of cuprous chloride and hydrochloric acid, to produce 2-chloro-11-[4-(2-hydroxyethyl) - 1 - piperazinyldibenz[b,f]-[1,4]oxazepine. The fumarate salt melts at 201°—204°C. when precipitated from ether and isopropanol.

Example 10

Preparation of 2-Bromo-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine

Using the procedure of Example 2, 2-amino - 11 - (4 - methyl - 1 - piperazinyl)-dibenz[b,f][1,4]oxazepine is diazotized, followed by decomposition in the presence of cuprous bromide and hydrobromide acid, and 2 - bromo - 11 - (4 - methyl - 1 - piperazinyl)-dibenz[b,f][1,4]oxazepine is obtained.

Example 11

Preparation of 2-Fluoro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine

Using the procedure of Example 2, 2-amino - 11 - (4 - methyl - 1 - piperazinyl)-dibenz[b,f][1,4]oxazepine is diazotized, followed by treatment with sodium fluoborate. The resulting diazonium fluoborate is isolated, and heated to effect decomposition to the product of 2-fluoro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine. The fumarate salt melts at 204°—205°C. when recrystallized from isopropanol.

Example 12

Preparation of 8-Chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine

When the procedure of Example 2 is repeated and 8-amino-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine is diazotized, followed by decomposition in the presence of copper powder and hydrochloric acid, the product 8-chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine is obtained.

Example 13

Preparation of 2,8-Dichloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine

Using the procedure of Example 1, 11-(4-methyl - 1 - Piperazinyl) - 2,8 - dinitrodibenz[b,f][1,4]oxazepine is reduced to the corresponding 2,8-diamino derivative, and this amino derivative is tetrazotized followed by treatment with cuprous chloride and hydrochloric acid, and 2,8-dichloro-11-(4-methyl-1 - piperazinyl)dibenz[b,f][1,4]oxazepine is obtained.

Example 14

Preparation of 2-Chloro-11-[N-methyl-(2-dimethylaminoethyl) amino]dibenz [b,f] [1,4]-oxazepine

Using the procedure of Example 2, 2-amino - 11 - [N - methyl - (2 - dimethylaminoethyl)amino]dibenz[b,f][1,4]oxazepine is diazotized, followed by decomposition in the presence of copper powder and hydrochloric acid, and 2-chloro-11-[N-methyl-(2-dimethylaminoethyl)amino]dibenz [b,f] [1,4] oxazepine is obtained.

Example 15

Preparation of 2-Bromo-11-[N-methyl-N-(3-dimethylamino - 2 - methylpropyl)amino]-dibenz[b,f][1,4]oxazepine

When the procedure of Example 2 is repeated and 2-amino-11-[N-methyl-N-(3-dimethylamino - 2 - methylpropyl)amino]-dibenz[b,f][1,4]oxazepine is diazotized, followed by decomposition in the presence of cuprous bromide and hydrobromic acid, the product 2 - bromo - 11 - [N - methyl - N - (3-dimethylamino - 2 - methylpropyl)amino-dibenz[b,f][1,4]oxazepine is obtained.

Example 16

Preparation of 11-[N-methyl-(2-piperidinoethyl)amino]dibenz[b,f][1,4]oxazepine

Using the procedure of Example 2, 2-amino - 11 - [N - methyl - (2 - piperidinoethyl)amino]dibenz[b,f][1,4]oxazepine is diazotized, followed by decomposition in the presence of hypophosphorous acid and 11-(N-methyl - 2 - piperidinoethylamino)dibenz-[b,f][1,4]oxazepine is obtained.

Example 17

Preparation of 2-Methoxy-11-[N-methyl-(2-morpholinoethyl)amino] dibenz [b,f] [1,4]oxazepine

When the procedure of Example 2 is repeated and 2-amino-11-[N-methyl-(2-morpholinoethyl)amino]dibenz [b,f][1,4] oxazepine is diazotized, followed by decomposition in the presence of methanol, the product 2-methoxy - 11 - [N - methyl - (2 - morpholinoethyl)amino]dibenz[b,f][1,4]oxazepine is obtained.

Example 18

Step (a)—Preparation of 2-Chlorodibenz-[b,f][1,4]oxazepin-11-(10H)-one

A solution of 2-nitrodibenz[b,f][1,4]-oxazepin-11(10H)-one is hydrogenated over platinum oxide in ethanol, filtered and concentrated to yield 2-aminodibenz[b,f][1,4]-oxazepin-11(10H)-one. This base dissolved in concentrated hydrochloric acid is treated at 0—5° with one equivalent of sodium nitrite and, when diazotization is complete with one equivalent of cuprous chloride—dissolved in concentrated hydrochloric acid. The mixture

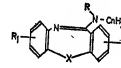
is then stirred at room temperature to complete evolution of nitrogen and formation of 2 - chlorodibenz[b,f][1,4]oxazepin - 11(10H)-one, which may be purified by conventional procedure. When purified by recrystallization from ethyl acetate, this product melts at 245—246°C.

Step (b)—Preparation of 2-Chloro-11-(4-methyl - 1 - piperazinyl)dibenz[b,f][1,4]-oxazepine

Crude 2-chloro-dibenz[b,f][1,4]oxazepin-11(10H)-one, prepared as described in Step (a) is treated with phosphorous pentachloride in anhydrous benzene. The mixture is refluxed until it becomes homogeneous, and an excess of N-methylpiperazine is added. Refluxing is continued until the reaction is substantially complete, and 2-chloro-11-(4-methyl - 1 - piperazinyl)dibenz[b,f][1,4]-oxazepine is thereby obtained. When purified this product melts at 108—111°C.

WHAT WE CLAIM IS:—

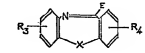
1. A process for preparing a compound of the formula:



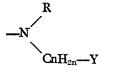
where X is oxygen or sulfur; one of R_3 and R_4 is hydrogen, (C_1—C_6) alkyl (C_1—C_6) alkoxy, halogen or trifluoromethyl, and the other of R_3 and R_4 is hydrogen, (C_1—C_6) alkoxy or halogen; Y is hydroxy, amino, (C_1—C_6) alkylamino, di-(C_1—C_6) alkylamino, 1-piperazinyl, 4-(C_1—C_6) alkyl-1-piperazinyl, 4-hydroxy (C_1—C_6) alkyl-1-piperazinyl, pyrrolidino, (C_1—C_6) alkyl-pyrrolidino, piperidino, (C_1—C_6) alkyl-piperidino, morpholino or (C_1—C_6) alkyl-morpholino; R is (C_1—C_6) alkyl; n is 2, 3 or 4; or the

group taken together represents 1-piperazinyl, 4-(C_1—C_6) alkyl-1-piperazinyl, or 4-hydroxy (C_1—C_6) alkyl-1-piperazinyl; which process comprises:

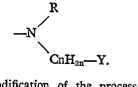
(a) diazotizing a compound of the formula:



wherein X is oxygen or sulphur; one of R_3 and R_4 is hydrogen, halogen, (C_1—C_6) alkyl, (C_1—C_6) alkoxy or trifluoromethyl, and the other of R_3 and R_4 is amino; and E is the group



wherein R, Y and n are as defined above, or a hydroxy, amino, di-(C_1—C_6) alkylamino or (C_1—C_6) alkylamino group; in the presence of a mineral acid with an alkali metal nitrite or alkaline earth metal nitrate, and subsequently treating the diazonium compound with a hydrohalic acid, a (C_1—C_6) alkanol or a reducing agent; and (b) when required, when E is hydroxy, amino, di-(C_1—C_6)alkyl amino or (C_1—C_6) alkylamino, before or after step (a), converting E into the group



2. A modification of the process defined in Claim 1, wherein both of R_3 and R_4 in the starting compound of Formula II are amino, to produce a compound of Formula I wherein R_3 and R_4 are each hydrogen, (C_1—C_6) alkoxy or halogen.

3. A process according to Claim 1 or Claim 2 wherein the diazotization is carried out at a temperature of from −25°C to 25°C.

4. A process according to any preceding Claim, wherein the diazonium compound is subsequently treated with a hydrohalic acid in the presence of a metal catalyst at a temperature of from 0° to 100°C.

5. A process according to any one of Claims 1—3, wherein the diazonium compound is subsequently treated with a (C_1—C_6) alkanol at a temperature of from 25° to 125°C.

6. A process according to any one of Claims 1—3, wherein the diazonium compound is subsequently treated with a reducing agent at a temperature of from 0° to 25°C.

7. A process according to Claim 1 and substantially as hereinbefore described.

8. An 11-tertiary-aminodibenz[b,f][1,4]-oxazepine or -thiazepine whenever prepared by a process according to any preceding Claim.

9. A pharmaceutical preparation comprising a compound as defined in Claim 8, and a pharmaceutically acceptable carrier or diluent therefor.

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